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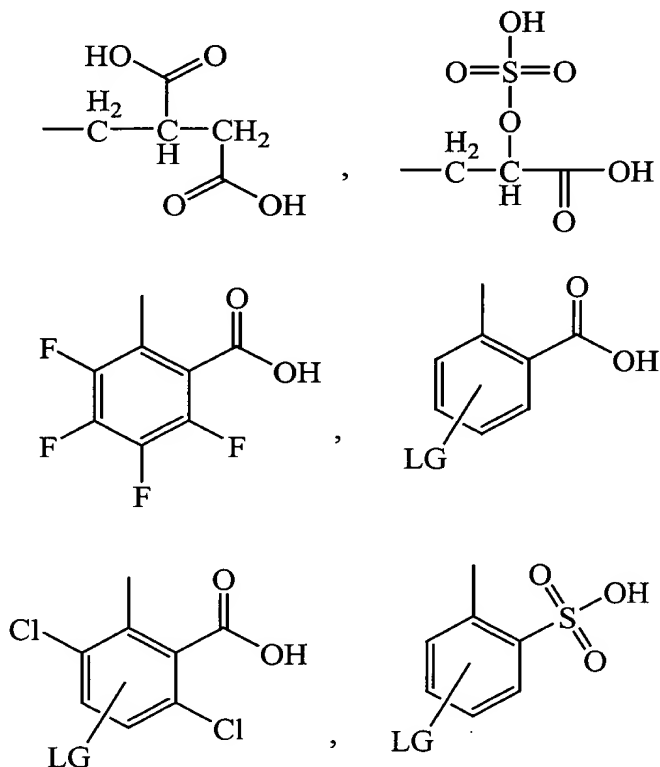
Reconsideration of the application is respectfully requested. By this Amendment, claims 62 and 65-75 have been cancelled without prejudice, and claims 46, 50, 53, 59, 60 and 64 have been amended. Accordingly, claims 46-61 and 63-64 are pending.

I. Amendments

Claim 46 has been amended to include Markush language and to clarify that certain substituents are selected independently of each other.

Claim 50 has been amended to read: The labelled nucleic acid compound of claim 46 wherein R_8 is alkyl independently substituted with one or more substituents selected from halogen, $-C(O)R$, and $-S(O)_2R$ wherein R is independently selected from $-OH$, O-alkyl, $-NH_2$, N-alkyl and a linking group. Support for linking group can be found in the specification at page 21, lines 9-14, for example.

Claim 53 has been amended to read: The labelled nucleic acid compound of claim 46 wherein R_8 is selected from the structures:



wherein LG is a linkage linking group. Support for LG in the structures and "LG is a linking group" can be in the specification at page 22, line 20 through page 23, line 1, for example.

Claims 59 and 60 have been amended to recite the phrase "to form the structure" in accordance with the Examiner's suggestion (see Office Action page 13, item 15(E)). Support for these amendments is inherent in the claims as originally presented, for example.

Claim 62 has been cancelled without prejudice, mooting the rejection of this claim.

Claim 64 has been amended to read: The labelled nucleic acid compound of claim 63 wherein L comprises an aminohexyl linking group, and NUC comprises a polynucleotide, wherein the aminohexyl linking group is attached to the polynucleotide at the 5' terminus. Support for "wherein L comprises an aminohexyl linking group" can be found in the specification at, for example, page 60, line 18 through page 61, line 9 and page 67, line 1. Support for "and NUC comprises a polynucleotide, wherein the aminohexyl linking group is attached to the polynucleotide at the 5' terminus" is inherent in the claim as originally presented.

Claim 65 has been cancelled without prejudice, mooting the rejection of this claim.

No new matter has been added by any of these amendments.

II. Restriction Requirement

Non-elected claims 66-75 have been cancelled without prejudice.

III. Claim Objections

The Examiner objected to Claim 55 because the claim did not end in a period. A period has been added to the end of Claim 55 at the Examiner's request.

The objections to claims 62 and 65 are moot in light of cancellation of those claims.

IV. Rejection Under 35 U.S.C. 112, First Paragraph: Claims 57, 62, 64 and 65

Claims 57, 62, 64 and 65 were rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking sufficient written description. The rejection is respectfully traversed.

Claim 57 has support in the specification at page 63 lines 7-14, for example. Accordingly, withdrawal of the rejection of claim 57 is respectfully requested.

Claim 64 recites a labelled nucleic acid compound of the present invention wherein L comprises an aminohexyl linking group, NUC is a polynucleotide and L is attached to the polynucleotide at the 5' terminus. This is supported in the specification at page 60, line 18 through page 61, line 9, page 66, line 20 and page 67, lines 1-3, for example. Withdrawal of the rejection is respectfully requested.

The rejections of claims 62 and 65 are moot in light of their cancellation.

V. Rejection Under 35 U.S.C. 112, First Paragraph: Claims 46-65

Claims 46-65 were rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking sufficient written description.. The Examiner suggested that the term "linkage" could "encompass an enormous variety of different entities", and that within the context of the specification, only limited examples of the preparation and use of such linkages are described. The rejection is respectfully traversed.

The applicants respectfully submit that the term "linkage" is adequately described in the specification so as to convey to one of skill that the applicants were in possession of the claimed invention at the time of filing.

The MPEP states that:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by...reduction to drawings, or by disclosure of relevant, identifying characteristics...sufficient to show the applicant was in possession of the claimed genus. (MPEP 2163 II(A)(3)(a)(ii))

The sufficiency of the specification is evidenced, in part, by the thorough discussion of what constitutes a linkage that begins at page 55 of the specification under the section heading V. A. Dye-Conjugate Linking Chemistry. This section describes what constitutes a linkage in the context of the invention, illustrates what a linkage does in the context of the invention, provides strategies for designing linkages for use in the present invention, and in Table I on pages 55-57 of the specification, presents a multitude of examples of linkages and routes to making the exemplified linkages.

In addition, further definition and discussion of the term "linkage" is provided throughout the specification. For example, on page 61, the specification provides a description of the general structure of a labeled nucleotide that includes what constitutes a linkage, how nucleotide labeling through such linkages can be carried out, and references that include exemplary nucleotide labeling procedures suitable for use in connection with the invention.

Finally, the Applicants have illustrated several specific examples of linkages by chemical structures on page 62 of the specification. Taken as a whole, the voluminous discussion and definition of the term "linkage" would clearly allow one skilled in the art to recognize that the Applicants were in possession of the invention at the time of filing.

Accordingly, withdrawal of the rejection is respectfully requested.

VI. Rejection Under 35 U.S.C. 112, First Paragraph: Claims 62 and 65

The Examiner has rejected claims 62 and 65 under 35 U.S.C. 112, first paragraph, for alleged lack of enablement. The rejection is moot in light of cancellation of these claims.

VII. Rejection Under 35 U.S.C. 112, First Paragraph: Claims 46-65

The Examiner has rejected claims 46-65 under 35 U.S.C. 112, first paragraph, for as allegedly lacking enablement. The rejection is respectfully traversed.

At the outset, the Applicants note that the Examiner has rejected Claims 46-65, *in toto*, and has not provided specific reasoning as to why each rejected claim allegedly lacks enablement. Absent such specific reasoning, the various rejections are extremely prejudicial to the Applicants, such that in order to be responsive, the Applicants must respond to rejections that are not articulated. The Applicants are thus forced to speculate as to why the Examiner might consider the claims non-enabled and respond to those speculations. However, it is the Examiner who bears the burden of establishing lack of enablement, not the Applicants. At a minimum, this burden requires the Examiner to provide reasoning sufficient to permit the Applicants to ascertain on what grounds each of the specified claims have been rejected.

Moreover, the Examiner's reasoning is in conflict with the rejection. In the first two paragraphs of item 13 of the Office Action, the Examiner indicates that compounds embraced by the claims are fully enabled. Specifically, the Examiner states that the specification is "enabling for compounds comprising defined linkage sites on the D moiety and a structurally defined linkage (L)", yet all of Claims 46-65 were rejected under 35 U.S.C. 112, first paragraph. Clearly, claims reciting these admittedly enabled compounds cannot be properly rejected for lack of enablement. Accordingly, Applicants submit that the rejection is improper and request that it be withdrawn for at least the foregoing reasons.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach what is well known in the art and preferably omits what is well-known to those skilled and already available to the public. See *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1986); *In re Buchner*, 929, F.2d 660, 661 18 USPQ2d 1331,1332 (Fed. Cir.1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986),

cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In the present case, the Applicants' original disclosure provides more than ample guidance for preparing various compounds comprising exemplary linkages, as discussed in Section V above. The Examiner has provided no reason or evidence why the relevant description is not enabled.

Applicants note that the Examiner has attempted to build the rejection using the factors first summarized by the board in *Ex parte Forman*, 230 USPQ 546, as a backdrop. However, in making a determination of lack of enablement, the burden is on the Examiner to consider *all* the evidence related to each of the factors, and any conclusion of nonenablement *must* be based on the evidence *as a whole*. And it is improper to conclude that a disclosure is not enabling based on an analysis ignoring one or more of the factors. *In Re Wands*, 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407. The Applicants submit that the Examiner has not carried the burden of fairly considering all of the relevant factors in making the determination of lack of enablement.

Further, the Examiner has previously held that "the level of skill would be high, most likely at the Ph.D. level". The Applicants submit that an individual at the Ph.D. level of skill in the relevant art would have a thorough knowledge of the state of the art. And upon reading the application as a whole with the state of the art as a back drop, including the guidance provided by the references incorporated within the specification, it would be clear to an average Ph.D. how to make and use the invention as claimed. In light of the teachings of the specification taken together with the knowledge accorded to one of ordinary skill in the art, it is respectfully submitted that the claimed invention could readily be implemented by one of ordinary skill in the art without undue experimentation. Accordingly, withdrawal of the rejection is respectfully requested.

VIII. Claim Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 46, 50, 53, 55, 60, 62 and 65 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. The rejections are respectfully traversed.

The rejection of claim 46 is moot in light of amendment to include Markush language.

The rejection of Claim 46 over the recitation of "analogous thereof" is respectfully traversed. The Examiner stated that it is unclear what would or would not comprise an

analog as claimed, and that the specification does not provide a standard for ascertaining such terms. The Applicants respectfully disagree. "Analog" in reference to nucleotides, nucleosides and polynucleotides is clearly defined beginning at page 14, line 12 of the specification, for example. The Applicants submit that the definition of analog is of such detail as to be clear to one of skill in the art. Accordingly, withdrawal of the rejection is respectfully requested.

The rejection of claims 50 and 53 are believed to be obviated by the present amendments to these claims.

The rejection claim 55 over the recitation of "phosphate analog" for substantially the same reasons as claim 46, above, is respectfully traversed. The Applicants submit that an adequate and clear definition of "analog" in reference to phosphate analogs is presented on page 14, starting at line 17. Accordingly, withdrawal of the rejection is respectfully requested.

The rejection of Claims 59 and 60 are believed to be obviated by the amendments adding the phrase "to form the structure".

The rejection of claims 62 and 65 are moot in light of their cancellation.

IX. FEE AUTHORIZATION and REQUEST FOR TIME EXTENSION

A Petition for a 3-Month Extension of Time is enclosed herewith. If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from Applied Biosystems Deposit Account No. 01-2213 (Order No. 4446D1).

Date: 4/30/03

Respectfully submitted,



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